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Is early virological response as predictive of the hepatitis C treatment response in dialysis patients as in non-uremic patients?

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SUMMARY

Objective: The aim of the present study was to determine whether hepatitis C virus (HCV) RNA present at week 12 is a good predictor of the response to interferon (IFN) monotherapy in hemodialysis patients with hepatitis C.

Methods: Hemodialysis patients with hepatitis C who were treated between 1997 and 2008 with IFN monotherapy for 48 weeks without dose reduction were included. The predictive value of HCV RNA at week 12 for achieving a sustained virological response (SVR) was determined.

Results: Forty patients (mean age 47 ± 9 years; 75% males and 80% with genotype 1) were included. Septal fibrosis or cirrhosis was observed in 38% of these patients. Twelve (30%) of the 40 patients achieved SVR. HCV RNA was undetectable at week 12 in 68%. The positive predictive value of HCV RNA at week 12 was 45% and the negative predictive value was 100%.

Conclusions: The presence of HCV RNA at week 12 had a high negative predictive value for SVR in hemodialysis patients with chronic hepatitis C treated with IFN for 48 weeks. Therefore, if HCV RNA is detected at week 12, treatment should be discontinued due to the low probability of a sustained response.

1. Introduction

Although the adoption of universal precaution methods has reduced the transmission of hepatitis C virus (HCV) among hemodialysis patients,[1] the prevalence of this infection has remained high in these patients compared to the general population. The prevalence of HCV infection also varies according to geographic region; the rates are less than 5% in northern European countries,[2] approximately 8% in the USA,[3] and as high as 70% in Saudi Arabia.[4] In addition, the prevalence of this infection varies widely between dialysis centers in the same country.

In Brazil, the Brazilian Society of Nephrology has conducted an annual census of patients on dialysis therapy since the beginning of this century. Data from the 2010 census, recently reported,[5] show that 340 of the 638 active dialysis centers answered the survey questions and information was obtained for 49 077 patients of the 92 091 estimated total number of patients on dialysis in the country. The prevalence of HCV infection among dialysis units was 5.8%, and fortunately it has been declining – the prevalence was 19.9% in 1999.[6]

The treatment of HCV in patients under renal replacement therapy is of critical importance. The impact of chronic hepatitis C infection in these patients is high, as recent observations have documented a greater probability of death due to liver cirrhosis, hepatocarcinoma, and cardiovascular disease in dialysis patients infected with HCV compared to uninfected subjects.[7,8] Furthermore, a large cohort study that compared the frequency of cancer among dialysis patients to that of the general population found a higher overall risk for cancer in these patients, which included the risk of liver cancer attributable to exposure to hepatitis B and C viruses.[9] Severe post-transplant complications of HCV infection, such as glomerulopathies, loss of renal grafts,[10,11] and a reduced 10- and 20-year survival rate,[12,13] have been demonstrated in HCV-positive kidney transplanted patients. In addition, kidney transplanted patients with hepatitis C showed higher morbidity and mortality due to liver disease than did immunocompetent patients with hepatitis C.[14]

As the post-transplant administration of interferon (IFN) has been associated with the risk of renal graft loss,[15–17] its administration is generally not recommended.[18] Instead, all efforts should be made to eradicate the infection before renal transplant.

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According to a recent meta-analysis,[19] the estimated sustained virological response (SVR; i.e., no detectable HCV RNA at 24 weeks after cessation of therapy) rate for hemodialysis patients who received conventional IFN monotherapy was 39%, which was greater than that estimated for immunocompetent patients. However, the low tolerance of these patients to IFN may lead to high rates of treatment discontinuation.[20] Despite the large number of studies evaluating the predictive value of HCV RNA during the early stages of treatment (weeks 4 to 12) for a sustained response in non-uremic patients,[21,22] this parameter has not been established in hemodialysis patients. This analysis would be useful because of the low tolerance of these patients to treatment.

The objective of the present study was to evaluate the predictive value of HCV RNA at week 12 in dialysis patients treated with conventional IFN for 48 weeks.

2. Methods

2.1. Patients

A retrospective study was conducted on hemodialysis patients with chronic hepatitis C (anti-HCV reactive and HCV RNA-positive) who were attended at the Hepatitis Unit of the Federal University of São Paulo between 1997 and 2008. Patients treated with conventional IFN monotherapy for 48 weeks and who had HCV RNA tests at week 12 of treatment and at week 24 post-treatment were selected for this study.

Patients infected with HIV and/or hepatitis B virus and those previously treated for hepatitis C or who had their treatment discontinued were excluded.

The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

2.2. Variables analyzed and determination of HCV RNA

The following variables were analyzed: gender, age, etiology of chronic renal disease, type of dialysis, history of kidney transplantation, time on dialysis, estimated duration of infection, alanine aminotransferase (ALT) level, stage of hepatic fibrosis, HCV genotype, and the presence of HCV RNA at week 12 of treatment and at week 24 post-treatment. The duration of infection was estimated based on the first year of dialysis or the year of the first blood transfusion if before 1992.

The HCV RNA content of stored serum samples (freezer temperature −20 °C) was determined by qualitative PCR (Cobas Amplicor HCV Test, Roche Diagnostic Systems, USA) using a detection limit of 50 IU/ml. The HCV genotype was determined by sequencing of the 5′-untranslated region.[23]

2.3. Therapeutic regimen

Treatment was indicated for patients whose liver biopsies showed interface hepatitis and/or the presence of stage 2 fibrosis, according to the Metavir classification.[24] The therapeutic regimen consisted of conventional IFN alpha-2a or IFN alpha-2b (3 000 000 IU, three times per week) for 48 weeks, which in all cases was administered following dialysis sessions.

2.4. Evaluation of virological response

An early virological response (EVR) to antiviral treatment is usually defined as partial (pEVR) when a ≥100-fold decrease in viral load occurs at week 12, and as complete (cEVR) when HCV RNA at week 12 is undetectable. In the present study the EVR was evaluated by qualitative HCV RNA level at week 12 (cEVR). Qualitative determination of HCV RNA 24 weeks after therapy was used for analysis of SVR. Per-protocol analysis was used to determine the response rate.

2.5. Statistical analysis

A descriptive analysis of the variables of interest was performed and the association between variables was determined. When indicated, categorical variables were compared using Fisher's exact test. The positive and negative predictive values of HCV RNA at week 12 for SVR were calculated. A level of significance of <0.05 was used. PASW 18.0 software (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis.

3. Results

A total of 113 patients were treated during the study period and 40 of these fulfilled the inclusion criteria. The other 73 patients were excluded from the study due to an early interruption/abandonment of treatment or a dose reduction in 31 patients (42%), the absence of serum for analysis at week 12 in 24 patients (33%), and the presence of HBV co-infection in 18 patients (25%). There was no difference between excluded and included patients regarding age, time on dialysis, stage of fibrosis, or genotype distribution.

The mean age of the 40 patients included in the study was 47 ± 9 years, and the majority of patients were male (75%). The time on dialysis ranged from 1 to 19 years (median of 6 years), and the main cause of known chronic renal disease was systemic arterial hypertension.

According to the Metavir classification for the staging of hepatic fibrosis on biopsy, it was absent in 5% of patients (stage 0), 57% patients had stage 1, 15% had stage 2, 13% had stage 3, and 10% had stage 4. The pretreatment epidemiological, clinical, and laboratory characteristics of the patients are shown in Table 1.

3.1. HCV RNA at week 12 and the sustained virological response

HCV RNA was undetectable at week 12 in 27 patients (68%), and the overall SVR rate was 30% (12/40). According to HCV genotyping performed in 26 patients, SVR was 24% in genotype 1, and the only

Table 1
Baseline demographic and clinical characteristics of the study patients (n = 40)

Characteristics	
Age, years, mean ± SD	47 ± 9
Male gender, n (%)	30 (75)
Hemodialysis/peritoneal dialysis, n	38/2
Time on dialysis, years, median (IQR)	6 (4–7)
Previous kidney transplant, n (%)	11 (28)
Etiology of kidney disease, n (%)	
Hypertension	14 (35)
Glomerulonephritis	3 (8)
Diabetes mellitus	2 (5)
Other/unknown	21 (52)
Duration of HCV infection, years, median (IQR)	8 (6–14)
HCV genotype, n (%)	
Type 1	21 (80)
Type 2	1 (4)
Type 3	2 (8)
Type 4	1 (4)
Type 5	1 (4)
Liver histology, n (%)	
Bridging fibrosis or cirrhosis	15 (38)
ALT (× ULN), median (IQR)	1.02 (0.62–1.63)
Hemoglobin (g/dl), mean ± SD	12 ± 1.5
Platelet count (× 10^9/l)	183.025 ± 72.318

ALT, alanine aminotransferase; HCV, hepatitis C virus; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

five patients with genotype non-1 were non-responders (one genotype 2, two genotype 3, one genotype 4, and one genotype 5).

Forty-five percent of patients with negative HCV RNA at week 12 achieved SVR. However, none of the patients with detectable HCV RNA at week 12 had SVR ($p = 0.004$), as shown in Figure 1. Thus the cEVR had a negative predictive value (NPV) of 100% and a positive predictive value (PPV) of 45%.

4. Discussion

This study showed that detectable HCV RNA at week 12 of treatment had a high NPV (100%) for SVR in dialysis patients with chronic hepatitis C given conventional IFN monotherapy for 48 weeks. HCV RNA was evaluated qualitatively at week 12, as this is the conventional strategy used to evaluate the early response to IFN monotherapy.[25] This analysis is important because hepatitis C dialysis patients require a special therapeutic approach. The consequences of chronic HCV infection in this population, which include decreased survival during the post-transplant period, enforce the need to eradicate the virus. However, prolonged therapy can cause severe side effects and can negatively impact the stability of these patients.

The low tolerance of patients with renal failure to hepatitis C treatment has been established and may be due to the greater bioavailability of the drug or associations with co-morbidities.[20,26–28] In the study by Rocha et al.,[20] mild to moderate side effects of IFN therapy were observed in almost all patients and included flu-like symptoms, bone marrow suppression, diarrhea, depression, dermatological alterations such as hair loss and itching, infections, and hypothyroidism. Furthermore, severe side effects that resulted in the discontinuation of treatment were seen in 24% of the patients. Severe side effects were also the cause of early treatment interruption in 19 of 37 hemodialysis patients treated with conventional IFN therapy.[26]

The six meta-analyses regarding the efficacy and tolerance of IFN treatment in dialysis patients with chronic hepatitis C confirm the low tolerance of this population. In early 2000, two of these studies[29,30] demonstrated a high rate of treatment discontinuation due to side effects (30% and 17%, respectively). These data were later confirmed by further meta-analyses conducted by Fabrizi et al.[19] and Gordon et al.[31] that reported dropout rates of 19% and 26%, respectively. In the most recent meta-analyses by Alavian and Tabatabaei[32] and Fabrizi et al.,[33] there were dropout rates of 29.7% and 23%, respectively, following peginterferon therapy.

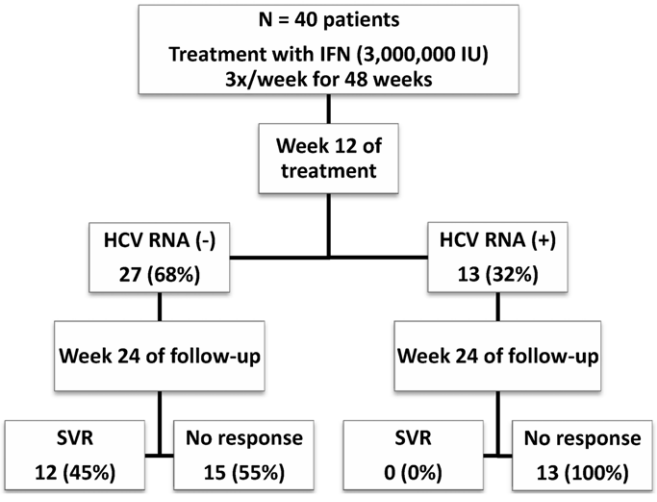

Figure 1. Sustained virological response (SVR) rates according to HCV RNA at week 12 of antiviral treatment with interferon (IFN).

Despite major advances in the treatment of chronic hepatitis C in the last decade, approximately a half of immunocompetent patients do not achieve sustained elimination of the virus with the current recommended therapeutic regimen (peginterferon and ribavirin).[34] Furthermore, this proportion is even greater (about 60%) among dialysis patients given pegylated or conventional IFN monotherapy.[19]

The factors associated with a positive response to antiviral treatment have been extensively studied in patients with normal renal function and include HCV genotype, stage of hepatic fibrosis, race, presence of steatosis/insulin resistance,[35–39] treatment compliance, ribavirin dose,[40,41] and viral kinetics.[35]

Over the last decade, studies have established the probability of a response to IFN treatment according to the kinetics of the HCV RNA level during therapy. For example, patients who did not achieve an EVR did not achieve SVR in 97% and 100% of cases,[21,22] which conferred a high negative predictive value to the presence of HCV RNA at week 12. The results from these studies favor the discontinuation of treatment in patients who do not achieve EVR at week 12 of treatment.

In regards of hemodialysis patients, Gordon et al.[31] showed that patients with lower rates of bridging fibrosis or cirrhosis, lower serum baseline HCV RNA levels, and infections with genotype non-1 tended to achieve higher SVR rates, although these findings did not reach statistical significance. However, that study included only baseline variables and did not allow for the interruption of treatment in patients with a lower likelihood of response. Therefore, the identification of HCV RNA during treatment is a highly attractive tool for the early identification of patients with a lower probability of response. Furthermore, this would indicate when therapy should be interrupted in this population in which the tolerance to treatment is significantly lower.

Studies on the kinetics of HCV RNA as a predictor of SVR in dialysis patients are scarce and have involved small numbers of patients. In addition, many studies are not comparable because they have evaluated different treatment regimens and HCV RNA at different periods. Furthermore, these studies have included patients with dose reductions and/or early treatment interruption, which can impair the analysis of the relationship between viral kinetics and SVR. Liu et al.[42] reported treatment failure in all patients who did not achieve a rapid virological response (undetectable HCV RNA at week 4 of treatment). In that study the patients received conventional or pegylated IFN monotherapy for 24 weeks. In another study that evaluated 37 hemodialysis patients,[26] conventional IFN monotherapy for 48 weeks was ineffective at inducing SVR in patients who had detectable HCV RNA in the second month of treatment. Finally, a study of only 12 patients showed that the SVR rate was influenced by the clearance of virus within the first 2 months of treatment.[43] Although insufficient to draw definitive conclusions, all these studies suggest that HCV RNA kinetics have a high predictive value for SVR. A recent meta-analysis by Gordon et al.[44] supports these data, as an association between SVR and viral negativity any time in the first 3 months of treatment was demonstrated.

The present study evaluated the predictive value of HCV RNA at week 12 of conventional IFN treatment in 40 dialysis patients. This group of patients was carefully selected from 113 dialysis patients treated for hepatitis C and included only patients treated for 48 weeks without dose reduction. Therefore, this study contributes data towards this unresolved issue. As we observed an NPV of 100%, these data show that the lack of cEVR is a strong indicator for the failure of IFN therapy in dialysis patients.

All patients received 48 weeks of treatment irrespective of HCV genotyping. The relationship between HCV genotype and treatment response in this special population has not yet been well established. In 2008 the Kidney Disease Improving Global

Outcomes (KDIGO) working group published guidelines with recommendations for the length of therapy based on HCV genotype (48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3) that were made by extrapolating data from the general population;[45] however these recommendations were not based on randomized clinical trials. In this context it is also very important to evaluate the predictive value of HCV RNA during very early weeks of treatment for patients with HCV receiving antiviral therapy for 24 weeks only.

The results of this study are meaningful due to the large number of co-morbidities and the high rate of potentially severe side effects of IFN treatment in this group of patients. Furthermore determining stopping rules for hemodialysis patients is extremely important for kidney transplant candidates because transplantation is delayed during IFN treatment. In conclusion, interruption of treatment should be indicated for hemodialysis patients with chronic hepatitis C on conventional IFN monotherapy who do not achieve a cEVR, due to the low probability of a response after 48 weeks.

Conflict of interest: The authors declare no conflict of interest.

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